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(54) Title: NEW COMBINATION FOR THE TREATMENT OF ASTHMA

(57) Abstract: An inhalation medicament comprising formoterol or a pharmaceutically acceptable salt thereof and beclomethasone dipropionate as a combined preparation is provided. Optionally, the medicament comprises also one or more pharmaceutically acceptable additives, diluents or carriers.



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NEW COMBINATION FOR THE TREATMENT OF ASTHMA

Field of the invention

5 The present invention relates to compositions useful in the treatment of asthma and other respiratory disorders. More particularly, it relates to inhalation compositions comprising a new combination of two pharmaceutically active substances.

Background of the invention

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Asthma is currently treated with drugs that can be classified into two classes, namely anti-inflammatory agents and bronchodilators. Anti-inflammatory drugs such as corticosteroids and sodium cromoglycate do not relieve asthma symptoms once they occur, rather they control the underlying inflammation. One of the drawbacks of anti-inflammatory drugs is that their onset of action is relatively slow. Therefore, patients often do not recognize any immediate therapeutic effects and tend to stop the medication. The acute asthma symptoms can be relieved by bronchodilators such as β_2 -adrenoreceptor agonists and theophylline. The short-acting inhaled β_2 -agonists, e.g. salbutamol and terbutaline, are important for an immediate symptomatic asthma relief, while long-acting β_2 -agonists, e.g. salmeterol, formoterol and procaterol, are important for treatment of moderate and severe asthma. However, there are currently still various debates on the safety of a regular use of β_2 -agonists as well as efficiency of long-acting β_2 -agonists.

25 Inhalation has become the primary route of administration in the treatment of asthma. This is because, besides providing direct access to the lungs, medication delivered through the respiratory tract provides rapid and predictable onset of action and requires lower dosages compared to the oral route. Typical delivery systems for inhalable drugs are the pressurized metered-dose inhaler (pMDI) comprising a suspension of fine drug particles in a propellant gas and the dry powder inhaler (DPI) comprising fine drug particles as dry powder typically admixed with coarser carrier or diluent such as lactose. Inhalable combinations of an anti-inflammatory agent and a bronchodilator have been described in patent publications EP 416950, EP 416951, WO 93/11773 and WO 98/15280.

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Despite recent advances in the understanding and treatment of asthma, there are still problems related to dosing regimens, systemic effects of the anti-asthma drugs and delivering fine drug particles deep into the lungs. Therefore improvements in the treatment of asthma and other respiratory disorders are desired.

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Summary of the Invention

It has been found that an inhalation medicament comprising formoterol or a pharmaceutically acceptable salt thereof and beclomethasone dipropionate, as a combined preparation, provides unexpectedly enhanced lung penetration of the active ingredients and enhanced therapeutic effect. Moreover, the combination shows improved stability of formoterol compared to formoterol in the absence of beclomethasone dipropionate. The combined preparation is therefore particularly useful in the treatment of asthma and other respiratory disorders.

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Accordingly, the present invention provides an inhalation medicament comprising formoterol or a pharmaceutically acceptable salt thereof and beclomethasone dipropionate as a combined preparation.

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The present invention also provides an inhaler device comprising an inhalation medicament comprising formoterol or a pharmaceutically acceptable salt thereof and beclomethasone dipropionate as a combined preparation.

25

Optionally, the medicament comprises also one or more pharmaceutically acceptable additives, diluents or carriers.

30

The active ingredients are preferably provided as micronized particles, e.g. having mass median diameter of less than 10 μm . Preferably, the medicament is provided in the form of dry inhalation powder comprising the active ingredients, optionally in admixture with carrier particles.

Detailed Description of the Invention

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The preferred salt of formoterol is formoterol fumarate, particularly in the form of dihydrate. Other suitable salts include acid addition salts of inorganic and organic acids, e.g. chloride, sulphate, tartrate, citrate, lactate and succinate salts or solvates thereof.

The active ingredients are preferably in the form of micronized particles, preferably having mass median particle diameter of less than about 10 μm , suitably from about 1 to about 5 μm .

5 The molar ratio of formoterol or a pharmaceutically acceptable salt thereof to beclomethasone dipropionate in a fixed combination is preferably from about 1:1 to about 1:1000, preferably from about 1:5 to about 1:100, more preferably from about 1:10 to about 1:60.

10 Preferably the medicament of the invention is in the form of a dry inhalation powder composition. Such compositions may be prepared e.g. by agglomeration of the micronized particles of the active ingredients and possibly the micronized carrier particles using methods known in the art.

15 It is particularly preferred that the dry inhalation powder composition is a mixture of the micronized particles of the active ingredients and carrier particles, the carrier particles being typically of coarser particle size. A method of preparing such mixtures typically comprises adding the micronized active ingredients and part of the carrier particles into a blender and mixing until the powder mixture is homogenous.
20 The mixture is then sieved to reduce the number of particle clusters present. Thereafter the rest of carrier particles is added and mixed until the powder is again homogenous.

 Particularly preferred carrier materials in dry inhalation powder compositions
25 are carbohydrates. Carbohydrates suitable for use as a dry powder carrier material include, for example, monosaccharides such as fructose, maltose or glucose; disaccharides such as lactose sucrose or trehalose; polysaccharides such as raffinose or melezitose; and alditols such as mannitol, xylitol, lactitol and the like. Preferred carrier is lactose or glucose, lactose being most preferred.

30 If the medicament contains a carrier, e.g. lactose, the total amount of the active ingredients is about 0.05 - 50 % (w/w), preferably about 1 - 10 % (w/w), based on total weight of the composition.

35 The mass median particle diameter of the carrier is preferably between 5 and 150 μm , more preferably between 10 and 100 μm , most preferably between 15 and 80 μm .

The medicament may alternatively be in the form of a pressurized aerosol where fine drug particles are suspended in a propellant gas. Examples of aerosol carriers include non-chlorofluorocarbon-based carriers such as HFA (hydrofluoro-
5 alkane). Pressurized aerosols can be prepared according to the methods well known in the art.

The medicament of the invention may also comprise additives such as solubilizers, stabilizers, flavouring agents, colorizing agents and preserving agents.

10

For administration by inhalation, the medicament according to the invention is conveniently delivered by conventional means. For example, the medicament can be delivered from inhaler devices well known in the art such as pressurized metered dose inhalers or dry powder inhalers. When the medicament is in the form of dry
15 inhalation powder, it can be filled in e.g. capsules, cartridges, blister packs or a reservoir, from which the powder may be administered by means of a dry powder inhaler.

The combination of the invention has a particular advantage in that the
20 inhaler device may comprise one or several parts made from polyacetal (POM) material, which normally is incompatible with formoterol due to the volatile components of polyacetal (POM) material. Polyacetal (POM) is frequently used in dry powder inhalers, e.g. in metering components, due to its advantageous mechanical properties.

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The medicament is preferably administered to provide a daily dose of from about 1 to about 100 µg, more preferably from about 6 to about 50 µg, of formoterol fumarate dihydrate and from about 50 to about 2000 µg, more preferably from about 100 to about 1000 µg, of beclomethasone dipropionate, depending on the age and
30 weight of the patient and the severity and type of the disease.

The medicament according to the invention may be administered to a patient daily or periodically, e.g. one month on treatment and one month off treatment. The medicament may be administered as divided doses from 1 to 4 doses a day.

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Although the plasma half-life of beclomethasone dipropionate is very short, its lung tissue binding half-life is 7.5 hours and consequently twice-daily administration is usually sufficient. For formoterol, the elimination half-life in plasma is around

10 hours and the duration of effect locally is over 12 hours, and the usual administration frequency is twice daily, too. Comparable durations of action locally and equal dosing schedules make beclomethasone dipropionate and formoterol ideal constituents for a fixed combination product.

5

The medicament suitably contains, per dose, from 3 to 36 µg, preferably from 6 to 24 µg, particularly from 12 to 24 µg, of formoterol fumarate dihydrate, and from 50 to 600 µg, preferably from 100 to 400 µg, particularly from 200 to 400 µg, of beclomethasone dipropionate.

10

For example, the medicament may contain, per dose, 12 µg of formoterol fumarate dihydrate and 200 µg of beclomethasone dipropionate. Administration of one to two such doses by inhalation twice daily would be effective in most cases of moderate persistent asthma and is likely to suffice in many severe asthmatics, too.

15

Lower dose strength containing, per dose, for example 6 µg of formoterol fumarate dihydrate and 100 µg of beclomethasone dipropionate would allow downward dose titration, once control is achieved and sustained for several weeks or months.

20

An example of a particularly preferred embodiment of the invention is an inhalation medicament in the form of dry inhalation powder comprising

a) formoterol or a pharmaceutically acceptable salt thereof having mass median particle diameter of less than about 10 µm, preferably from about 1 to about 5 µm;

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b) beclomethasone dipropionate having mass median particle diameter of less than about 10 µm, preferably from about 1 to about 5 µm; and

c) carrier having mass median particle diameter between 5 and 150 µm, preferably between 10 and 100 µm, more preferably between 15 and 80 µm, wherein the molar ratio of formoterol or a pharmaceutically acceptable salt thereof to beclomethasone dipropionate is from about 1:1 to about 1:1000, preferably from about 1:5 to about 1:100, more preferably from about 1:10 to about 1:60.

30

In the above embodiment, the amount of formoterol or a pharmaceutically acceptable salt thereof is preferably 0.01 – 5 %, more preferably 0.05 - 1 %, by weight of the composition; the amount of beclomethasone dipropionate is preferably 0.1 - 50 %, more preferably 0.5 - 10 %, by weight of the composition; and the

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amount of the carrier is preferably 50 - 99.9 %, more preferably 90 – 99.5 %, by weight of the composition.

5 The combination of the invention is useful in the treatment of asthma and other respiratory diseases, such as mild, moderate and severe asthma, allergic and non-allergic asthma, acute condition of asthma, intermittent asthma, episodes in chronic asthma, chronic obstructive pulmonary disease and adult respiratory distress syndrome. The treatment may be symptomatic or prophylactic treatment.

10 The invention is further illustrated by the following examples and experiments, which are not meant to limit the scope of the invention.

Example 1. Dry inhalation powder (per dose)

15	Formoterol fumarate dihydrate (micronized)	12 µg
	Beclomethasone dipropionate (micronized)	200 µg
	Lactose monohydrate Ph. Eur.	8 mg

20 Micronized active ingredients and part of the lactose were added into a blender. The powder mixture was mixed until it was homogenous. The mixture was then sieved to reduce the number of particle clusters present. Thereafter the rest of lactose was added and the powder was again mixed until it was homogenous. Powder was poured into the supply chamber of the multi-dose powder inhaler Easyhaler (Orion Corporation trademark) for a supply of 200 doses.

25

Experiments

Experiment 1.

30 Three dry powder formulations were prepared by blending micronized formoterol fumarate, micronized beclomethasone dipropionate and lactose monohydrate in the proportions given in Table 1.

Table 1. Dry powder formulations used in the Experiments. The values mean weight of the ingredient (g) per 1 g of total formulation.

Formulation	A	B	Combination
Formoterol fumarate dihydr.	0.006	-	0.0015
Beclomethasone diprop.	-	0.02625	0.02625
Lactose monohydrate Ph.Eur.	0.994	0.97375	0.97225
Batch size	0.8 kg	40 kg	0.2 kg

5 The homogenous formulations were filled into Easyhaler (Orion Corporation trademark) multi-dose dry powder inhalers. The dose metered by the inhaler (size of the metering cup) was four times smaller for formulation A than for other formulations.

10 The fine particle fraction of the active ingredients obtained from the inhalers filled with the formulations of Table 1 were determined using Twin Impinger as described in European Pharmacopoeia Supplement 2000. The results are shown in Table 2.

15 Table 2. Fine particle fraction of the active ingredients calculated from theoretical doses (200 µg for beclomethasone dipropionate and 12 µg for formoterol fumarate)

	A	B	Combination
Formoterol fumarate	44 %	-	39 %
Beclomethasone diprop.	-	40 %	63 %

20 The results show that the fraction of beclomethasone dipropionate particles having ability to reach deep into the lung (fine particle fraction) was superior in the combination medicament while there was no marked difference in the fine particle dose of formoterol fumarate between the formulations.

Experiment 2.

The stability of formulations "A" and "Combination" as described above were studied.

5

Packaging materials for both inhalation powders were multi-dose powder inhaler device, Easyhaler (Orion Corporation trademark), in laminate pouch (PTE/AL/PE, heat sealed). The material of the metering cylinder was ¼ A and 1A polyacetal (POM). POM is particularly suitable for use as metering cylinder material but is also known to be incompatible with formoterol fumarate dihydrate causing degradation product at retention times of 6.7min, 7.1 min and 8.2 min. The main impurity at 6.7 min was identified as N-methyl-formoterol. The following peak at 7.1 min contained two components with molecular ions at m/z 328 and 386. Impurity at 8.1 min showed molecular ion at m/z 493.

15

Storage time and conditions as well as stability results are presented in Tables 3 and 4.

Table 3. Stability results for Formoterol EH12µg/dose and Beclomethasone/-formoterol EH 12 µg/200 µg/dose inhalation powders. Storage condition 25°C/60% RH.

20

Degradation products	Specification	Formoterol EH			Beclomethasone/Formoterol EH		
		Initial	6 months	12 months	Initial	6 months	12 months
Rt 6.7 min	Max 0.1%	blq	0.13	0.137	blq	0.097	blq
Rt 7.1 min	Max 0.1%	blq	0.12	blq	blq	blq	0.069
Rt 8.2 min	Max 0.1%	blq	blq	0.147	blq	0.051	0.064

Blq = Below limit of quantitation (0.05%)

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Table 4. Stability results for Formoterol Easyhaler 12µg/dose and Beclomethasone/formoterol 12 µg/200 µg/dose inhalation powders. Storage condition 30°C/60% RH.

5

Degradation products	Specification	Formoterol EH				Beclomethasone/Formoterol EH			
		Initial	3 months	6 months	12 months	Initial	3 months	6 months	12 months
Rt 6.7 min	Max 0.1%	blq	0.128	0.171	0.250	0.037	0.082	0.101	blq
Rt 7.1 min	Max 0.1%	blq	0.140	0.172	0.04	blq	blq	blq	0.055
Rt 8.2 min	Max 0.1%	blq	blq	blq	0.222	blq	0.051	0.077	0.014

Blq = Below limit of quantitation (0.05%)

At 25°C/60% RH Formoterol EH 12 µg/dose inhalation powder has stability problem and the specification limits for the degradation products were exceeded. In contrast, Beclomethasone/Formoterol 200/12µg/dose inhalation powder shows good stability profile and the specification limits for the degradation products were not exceeded (Table 3).

At 30°C/60% RH Formoterol 12µg/dose inhalation powder contains degradation products exceeding the specification limits as early as after 3 months storage. On the other hand, Beclomethasone/Formoterol 200/12 µg/dose inhalation powder has good stability profile without any significant exceeding of specification limits (Table 4).

20

In conclusion, formoterol fumarate dihydrate was significantly more stable with beclomethasone in lactose blend than alone in lactose blend in the inhaler device.

Claims

1. Inhalation medicament comprising formoterol or a pharmaceutically acceptable salt thereof and beclomethasone dipropionate as a combined preparation.
2. Inhalation medicament according to claim 1 additionally comprising one or more pharmaceutically acceptable additives, diluents or carriers.
3. Inhalation medicament according to claim 1 or 2, wherein the pharmaceutically acceptable salt of formoterol is formoterol fumarate.
4. Inhalation medicament according to any of claims 1 to 3, wherein formoterol or a pharmaceutically acceptable salt thereof and beclomethasone dipropionate are in the form of micronized particles having mass median diameter of less than 10 μm .
5. Inhalation medicament according claim 4, in the form of dry inhalation powder.
6. Inhalation medicament according to claim 5, wherein formoterol or a pharmaceutically acceptable salt thereof and beclomethasone dipropionate are in admixture with a carrier.
7. Inhalation medicament according to claim 6, wherein the carrier is lactose.
8. Inhalation medicament according to any of claims 1 to 7, wherein the molar ratio of formoterol or a pharmaceutically acceptable salt thereof to beclomethasone dipropionate is from 1:1 to 1:1000, preferably from 1:5 to 1:100, more preferably from 1:10 to 1:60.
9. An inhaler device comprising inhalation medicament according to any of claims 1 to 8.
10. An inhaler device according to claim 9, which is a dry powder inhaler.
11. An inhaler device according to claim 9 or 10, wherein the inhaler device comprises one or several parts made from polyacetal (POM) material.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/14 A61K9/12 A61K31/57 A61K31/165 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

PAJ, EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 030 604 A (TROFAST JAN) 29 February 2000 (2000-02-29) column 2, line 3 - line 7 column 2, line 50 - line 58 abstract; claims 1,2,6,14-21,31,32; examples 1,7 ---	1-11
X	WO 98 41193 A (SCHERING CORP) 24 September 1998 (1998-09-24) page 8, line 39 - page 9, line 30 page 16, line 21 - line 28 abstract; claims 4,38,39,46-51 ---	1-11
E	EP 1 157 689 A (CHIESI FARMA SPA) 28 November 2001 (2001-11-28) claims; example 5 --- -/-	1-3

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 6 251 368 B1 (AKEHURST RACHEL ANN ET AL) 26 June 2001 (2001-06-26) column 5, line 29 - line 35 claims 8,11; example 23 -----	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/FI 01/00854

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6030604	A	29-02-2000	US 6287540 B1	11-09-2001
			AU 731192 B2	29-03-2001
			AU 5785998 A	07-08-1998
			BR 9811249 A	05-09-2000
			CZ 9902557 A3	13-10-1999
			EE 9900295 A	15-02-2000
			EP 1007017 A1	14-06-2000
			HU 0000714 A2	28-08-2000
			JP 2001508793 T	03-07-2001
			NO 993539 A	20-09-1999
			PL 334527 A1	28-02-2000
			WO 9831352 A1	23-07-1998
			SK 95999 A3	18-01-2000
			TR 9901690 T2	21-09-1999
			ZA 9800078 A	20-07-1998
			US 5980949 A	09-11-1999
			US 5983956 A	16-11-1999
WO 9841193	A	24-09-1998	AU 6537898 A	12-10-1998
			CN 1257423 T	21-06-2000
			EP 0969816 A1	12-01-2000
			HU 0002029 A2	28-11-2000
			JP 2000510478 T	15-08-2000
			NO 994519 A	19-11-1999
			PL 335742 A1	08-05-2000
			SK 128099 A3	12-06-2000
			WO 9841193 A1	24-09-1998
			ZA 9802254 A	17-09-1998
EP 1157689	A	28-11-2001	WO 0189480 A1	29-11-2001
			EP 1157689 A1	28-11-2001
US 6251368	B1	26-06-2001	US 5676929 A	14-10-1997
			US 6238647 B1	29-05-2001
			US 6303103 B1	16-10-2001
			AU 663904 B2	26-10-1995
			AU 3085092 A	19-07-1993
			BG 62119 B1	31-03-1999
			BG 98803 A	28-02-1995
			DE 69224656 D1	09-04-1998
			DE 69224656 T2	23-07-1998
			DK 616523 T3	28-09-1998
			EP 0616523 A1	28-09-1994
			EP 0990437 A1	05-04-2000
			HK 1004711 A1	28-07-2000
			JP 3026840 B2	27-03-2000
			JP 7502033 T	02-03-1995
			NO 942185 A	10-06-1994
			NO 20001227 A	10-06-1994
			RU 2129424 C1	27-04-1999
			SK 67494 A3	08-03-1995
			US 5674472 A	07-10-1997
			AP 402 A	22-08-1995
			AT 163539 T	15-03-1998
			AT 201587 T	15-06-2001
			BG 102689 A	26-02-1999
			CA 2125667 A1	24-06-1993
			CZ 9401430 A3	15-03-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/FI 01/00854

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6251368	B1	DE 69231857 D1	05-07-2001
		DE 69231857 T2	29-11-2001
		DK 756868 T3	10-09-2001
		WO 9311743 A1	24-06-1993
		EP 1066828 A1	10-01-2001
		EP 0756868 A2	05-02-1997
		ES 2113444 T3	01-05-1998
		ES 2158988 T3	16-09-2001
		HU 67534 A2	28-04-1995
		HU 9500331 A3	28-09-1995
		IL 104068 A	30-10-1998
		JP 11310533 A	09-11-1999
		MX 9207205 A1	01-11-1993
		NZ 246044 A	26-01-1996
		OA 9926 A	15-09-1994
		SG 74042 A1	18-07-2000
		US 5674471 A	07-10-1997
		US 5658549 A	19-08-1997
		US 5683676 A	04-11-1997
		US 5653962 A	05-08-1997
		ZA 9209617 A	22-03-1994
		AT 171865 T	15-10-1998
